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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/649,457	CRYSTAL ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *15 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-21 and 42-58* is/are pending in the application.

4a) Of the above claim(s) *2,3,11,12 and 42-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-10,13-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Matters

1. Applicant's request for reconsideration in the reply filed 01/15/2007 is noted. The Finality of the office action dated 11/152006 is withdrawn and prosecution is hereby reopened. New grounds of rejection are set forth below.

Status of Claims

2. Claims 1-3, 6-19, 21, and 42-58 are pending. Claims 4-5 and 21-41 were previously canceled and claims 2, 3, 11, 12, and 42-57 are withdrawn as non-elected subjected matter. Claims 1 and 7 are currently amended and claim 20 was canceled by Applicant's Response, filed 1/15/2007. Claim 58 was newly added and withdrawn by Applicant's Response, filed 1/15/2007.

Election/Restrictions

3. Applicant's election with traverse of the election by original presentation resulting in the withdrawal of claims 2, 3, and 42-57 in the reply filed on 11/15/2006 is acknowledged. Briefly claims 2 and 3 were amended to no longer recite the elected species of PA and thereby recited a gene vector further comprising a gene encoding edema factor and lethal factor, which are two embodiments that were not elected Applicant when the original restriction was issued and made FINAL, in the Non-Final

Rejection, mailed 5/19/2006. Claims 42-57 were newly added and are drawn to a method that does not require the vector of the elected invention. As claimed, the vector of the instant invention only comprised a coding sequence and a sorting signal and was considered a subcombination of the vectors that would be used in the method of claims 42-57. The traversal is on the ground(s) that a search of edema factor and lethal factor would not be a burdensome search because a search of protective antigen will result in relevant art for edema factor and lethal factor and that all of the transfer vectors encompassed by the claimed invention would function in a method of claims 42-57. This is not found persuasive because as previously stated in the non-final rejection, mailed 5/19/2006, an additional search of amended claim 2 and 3 would require a different search strategy than in their original presentation with a species election of PA. For example, now a search of gene vector with PA with edema factor with lethal factor would be required in multiple databases whereas the original search only required gene vector and PA. Therefore, the additional searching in multiple databases as would be required is considered undue. In terms of the methods of claims 42-57, the vector of claim 1 only encompasses a coding sequence and a signal sequence with no requirement of a promoter or elements necessary for expression as is required for a method of inducing an immune response would require. Therefore, only the subcombination of the vector of claim that includes regulatory elements would function in this method of claim 42-57 and therefore it is a distinct subcombination of claims 42-57.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2, 3, and 42-57 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject mater, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/15/2007.

Claim Objections

4. Claim 7 was object to for encompassing non-elected subject matter. Applicant amended the claims to remove the non-elected subject matter; therefore the objection is withdrawn.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

5. Amended claim 20, objected to under 37 CFR 1.75 as being a substantial duplicate of claim 15, has been canceled rendering the previous objection moot.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 6-10, and 13-21, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, have been amended and the rejection is withdrawn.

Amended claim 1 recited comprises a nucleic acid and a heterologous sorting signal, "wherein the nucleic acid sequence comprises SEQ ID NO:1." The metes and bounds of this recitation were deemed indefinite because it is not clear if the heterologous sorting signal is in addition to the processing and sorting signal already encompassed in SEQ ID NO:1 or if the heterologous sorting signal is in addition to SEQ ID NO:1. Applicant amended the claims to no longer include this recitation and now is deemed definite. Therefore, the rejection of claim 1 and its dependent claims 6-10 and 13-21 are withdrawn.

7. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "the exotoxin". There is insufficient antecedent basis for this limitation in the claim.

Claim 7 depends upon claim 6, which has been deemed indefinite and therefore renders dependent claim 7 indefinite.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

8. Claims 1, 6-10, and 13-19, and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention is drawn to a gene transfer vector comprising a nucleic acid encoding a humanized protective antigen sequence (hPA) of SEQ ID NO:1, heterologous sorting signal, and a heterologous signal peptide.

When the claims are analyzed in light of the specification, the instant invention encompasses a nucleic acid encoding a heterologous sorting signal and a heterologous signal peptide. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. While the specification mentions prophetically a nucleic acid encoding signal peptides and sorting signals that direct proteins to different intercellular compartments or makes a protein secretable, the only

example of a heterologous sorting signal or signal peptide that they provide are LAMP-1 for both an example of a heterologous sorting signal and a signal peptide. Therefore because the specification only discloses one species for a heterologous sorting signal and a heterologous signal peptide, LAMP-1, the specification does not teach the complete structure of a representative number of species of the claimed genus that comprises a heterologous sorting signal and signal peptide.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant characteristics, specified features and functional attributes that would distinguish different members of the claimed genus. The specification teaches that heterologous sorting signals direct proteins to subcellular sorting pathways such as extracellular, lysosomal, endoplasmic reticulum pathways (p. 16, [0040]). The specification teaches that LAMP-1 is a type I transmembrane protein that localizes predominantly to lysosomes and late endosomes, therefore the lysosomal pathway (p. 16, [0042]). The specification also teaches that signal peptides also target proteins to specific cellular compartments, but unlike sorting signals, which can comprise a portion of the mature protein in which they are found, signal peptides typically are removed from a precursor polypeptide and thus are not present in the mature protein (p. 15, [0039]). While the specification does disclose some special features of a LAMP-1 sorting signal and some general characteristics of heterologous sorting signals and heterologous signal peptide, it does not provide special distinguishing feature for the whole genera. Therefore, a representative number of species have not been sufficiently described by other relevant characteristics, specified

features and functional attributes in the specification as required by the written description requirement.

In conclusion, given the breadth of the genus, species have not been sufficiently described by other relevant characteristics, specified features and functional attributes, and the limited number of examples provided, and given that no specific identifying features/characteristic of species of the genus, were provided, the written description requirement disclosing the complete structure of genus comprising heterologous sorting signal and heterologous signal peptide has not been met. Furthermore, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of the genus comprising heterologous sorting signal and heterologous signal peptide, at the time the application was filed.

Enablement

9. Claims 1, 6-10, and 13-19, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification,

while being enabling for:

An adenoviral gene transfer vector of serotype 5 comprising a nucleic acid sequence of SEQ ID NO:1 encoding a secretable *B. anthracis* protective antigen comprising human-preferred codons (hPA) and further comprising a nucleic acid sequence encoding a cleavable lysosomal-associated membrane protein –1 sorting signal (LAMP-1) that targets a protein encoded by the said nucleic acid to the lysosomal pathway, operably linked to the CMV EI promoter-enhancer.

does not reasonably provide enablement for:

An adenoviral gene transfer vector comprising a nucleic acid of SEQ ID NO:1 and further comprising 1) any heterologous sorting signal or signal peptide that traffics the encoded protein to any cellular pathway, and 2) lacking a promoter sequence, 3) wherein the gene transfer vector transduces antigen presenting cells, and 4) a pharmaceutical composition comprising said gene transfer vector and a pharmaceutically acceptable carrier.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use/make the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification teaches the construction of an E1 deficient, serotype 5 adenoviral vector comprising a the nucleic acid sequence of SEQ ID NO:1 encoding a secretable immunogenic portion of *B. anthracis* protective antigen comprising human-preferred codons (hPA) and a cleavable lysosomal-associated membrane protein –1 sorting signal (LAMP-1), operably linked to the CMV IE promoter-enhancer (Example 1, pages 26 and 27, [0075]). The specification also teaches that the intended use of the instant vector is as a DNA vaccine to elicit an immune response against *B. anthracis* protective antigen (p. 1, [002]) and that the heterologous sorting signal is meant to direct the encoded hPA to subcellular pathways that are involved in antigen presentation to elicit a humor immune response (p. 16, [0041]). The specification also teaches that LAMP-1 is involved in directing proteins, such as the hPA, to the lysosomal compartment in host cells such that the directed protein is presented by MHC II peptides at the cell surface, thereby eliciting a humoral immune response against the directed protein (p. 16, [0042]). The specification also teaches that the above disclosed adenoviral gene transfer vector was administered to C57Bl/6 mice intramuscularly and that two weeks post-injection anti-PA antibodies were present in the mice immunized with the gene transfer vector as measure by ELISA (Example 1, page 27, [0075]).

However, the specification does not support the full breadth encompassed by the claims.

1) The breadth of the claims encompass any heterologous sorting signal or signal peptide that traffics the encoded protein to any cellular pathway. However, the specification teaches that the claimed vector is meant to elicit and immune response. Therefore, if the protein had a heterologous sorting signal the directs that any cellular compartment that is not involved in antigen presentation, such as the lysosomal pathway, then it will not function as a DNA vaccine as intended. Therefore, an artisan would not know how to use a gene transfer vector as a DNA vaccine that encodes any other heterologous sorting signal than one that directs the protein to one that is involved in antigen presentation.

Furthermore, the art teaches that the production of fusion proteins to target antigen presenting cells has widely variable means of success depending on the targeting portion of the fusion protein and the species that is immunized. Van Drunen Little-van den Hurk et al (Immunol Rev 199:113-125: 2004) teach that a gene vector encoding a 45W antigen from *Taenia ovis* fused to a CLTA4 targeting polypeptide administered to mice elicited an immune response where as the 45W-L-selectin did not. However, when the 45W-CLTA4 construct was administered to sheep, it did not elicit an immune response (p. 119, col 2 par bridging col 1 and 2). Ultimately, Van Drunen Little-van den Hurk et al (p. 120, col 1, lines 4-6) concluded that "targeting to APC has this far not been effective in natural host species." Therefore, the art suggest that gene transfer vectors that encode fusion protein that have a targeting region that is meant to target it

for antigen presentation and to antigen presenting cell as is the case in the instant invention with the claimed heterologous sorting signals are unpredictable in the art. To overcome this unpredictability in the art, an artisan would look to the specification for specific guidance as to which targeting sequences and heterologous sorting signals will be functional in a DNA vaccine. However, the specification only provides LAMP-1 as a sorting signal that has been shown to be operable in the instant invention; therefore, the specification only enables LAMP-1 as a sorting signal.

2) The instantly claimed gene transfer vector does not require a promoter. However, for a gene therapy vector to be expressed effectively it must minimally comprise the elements to be directed by the transcription and translation machinery of the target cell which require a promoter capable of driving expression in a cell. In the instant case, the specification discloses an adenoviral vector comprising the coding sequence for hPA-LAMP-1 operably linked to the CMV IE promoter-enhancer. These elements resulted in the expression of hPA-LAMP-1. However, the instant claims only disclose the hPA coding sequence and the heterologous sorting signal coding sequence for LAMP-1. Because of the necessity for the minimal elements necessary to drive expression of a gene, an artisan would not know how to use a nucleic acid encoding hPA-LAMP-1 without operable linkage to a promoter as a DNA vaccine as indented.

3) A narrowing embodiment of the invention is drawn to the gene transfer vector wherein it transduces antigen-presenting cells. However, the specification does not teach any means by which the gene transfer vector will target and deliver the vector to specifically transduce antigen presenting cells in vivo. Van Drunen Little-van den

Hurk et al teach (p. 119, col 2, last par), "Although APCs are critical for the induction of an immune response, the chance that APCs are transfected is relatively small." Therefore, since neither the specification nor the art support the general capability of a vector that has no means of targeting the vector for the specific transduction of antigen presenting cells, the instant invention is not enabled for this embodiment.

4) The instant invention encompasses a pharmaceutical composition comprising the claimed vector. The state of the art of DNA vaccination is unpredictable. Van Drunen Little-van den Hurk et al teach (page 114, col 1, last 6 lines and 1st line col 2), "Although the concept of DNA immunization has been proven to be extremely successful in inducing immune response in mice, significant barriers exist to effective induction of immunity in large animal and humans using DNA immunization. Indeed, there is not one DNA vaccine that has been approved for human or veterinary use. This lack is mainly due to their relatively low efficiency, specifically in target species."

Because of this low efficiency and unpredictability of DNA vaccine vectors to produce immunity, an artisan would look to the specification for specific guidance on making a vector that can be used as a pharmaceutical and produce immunity in a host. The specification as discussed above does demonstrate that the instant vector did elicit the production of anti-hPA antibodies. However, the specification does not teach that the instantly claimed vector resulted in a protective immune response. Therefore, an artisan would not know if the instantly claimed vector could be used as a pharmaceutical as claimed. Furthermore, for an artisan to use the instant gene transfer vector in a pharmaceutical composition, they would have to do further research such as

challenge the immunized mice with anthrax to determine if the immune response is protective and would further have to do the same type of testing in other species besides mice to see if it would be effective as a pharmaceutical composition. This level of empirical experimentation would be considered undue. Therefore, the instant specification only enable a gene transfer vector and not a pharmaceutical composition as claimed.

Therefore, due to the unpredictability in the art and the lack of specific guidance to support the full breadth of the claimed invention, the instant invention is only enabled for An adenoviral gene transfer vector of serotype 5 comprising a nucleic acid sequence of SEQ ID NO:1 encoding a secretable *B. anthracis* protective antigen comprising human-preferred codons (hPA) and further comprising a nucleic acid sequence encoding a cleavable lysosomal-associated membrane protein –1 sorting signal (LAMP-1) that targets a protein encoded by the said nucleic acid to the lysosomal pathway, operabley linked to the CMV EI promoter-enhancer.

Conclusions

10. As previously made of record, SEQ ID NO:1 encodes a novel humanized protective antigen that is free of the art. However, because of the breadth of the claims not all aspects of the claim vector comprising SEQ ID NO:1 are enabled for their intended use as a DNA vaccine.

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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